

# THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

## Rhythms of life **TIMING IN ENDOCRINOLOGY**



Special features  
**PAGES 6-17**

Bringing the  
best to Brighton  
**SfE BES 2019**

**P22**

An agent of change:  
**THE ENDOCRINOLOGY CRG**

**P30**

**WORKING  
TOGETHER**

Achievements of 2019

P18

**CELEBRATING  
SUCCESS**

Society Committees in 2019

P24

**INTERDEPARTMENTAL  
PEER REVIEW**

A nurse's view

P29

## A word from THE EDITOR...



The need to adapt to environmental changes has necessitated biological timing in all organisms. Understanding these rhythms underpins the diagnosis and treatment of many endocrine conditions. We have therefore dedicated the winter issue of *The Endocrinologist* to 'timing in endocrinology'.

In this issue, we have gathered articles from a wide range of expert contributors. Sasha Howard describes why the timing of puberty is changing and why it matters. Thomas Upton outlines the importance of glucocorticoid pulsatility. Kugajeevan Vigneswaran and Sesh Kamal Sunkara examine some of the time-related concepts in reproductive medicine and consider the challenges faced by healthcare professionals working in the field of infertility. David Ray highlights the need to embrace the biology of the circadian clock to enhance diagnostics and therapeutics for widespread human benefit.

Aimee Di Marco and Fausto Palazzo discuss the optimal timing of parathyroid surgery in pregnancy. Louise Hunter writes about circadian misalignment and metabolic health. Finally, Anneke Graf reminds us that the pulsatile nature and rhythmic pattern of hormone secretion can have important implications for ordering and interpreting endocrine investigations.

It has been a pleasure for me to work with a great team at the Society for Endocrinology as the Editor of *The Endocrinologist*. As I approach the end of my term, I am delighted to hand over to Helen Simpson, who has already been making an important contribution to the magazine as Associate Editor.

With warmest wishes and season's greetings

AMIR SAM

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## CONTENTS

You can view this issue online:  
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### ON THE COVER...

# P6-17

## TIMING IS EVERYTHING

The hormonal rhythms of life

# P22-23

## SfE BES 2019

Bringing the best to Brighton

### HEADLINES

- 3** Welcoming your new President  
Society events and opportunities  
New co-Editor-in-Chief for journals  
Plus dates and deadlines

### HOT TOPICS

- 4** The latest endocrine research

### SOCIETY NEWS

- 18** 2019 - a year of achievement
- 20** Society journals at the forefront

- 22** Brilliance in Brighton
- 24** Society committees: working for you in 2019
- 28** Strengthening your clinical practice

### NURSES' NEWS

- 29** Phillip Yeoh on interdepartmental peer review

### GENERAL NEWS

- 30** An agent of change: the Clinical Reference Group

### FEATURES

- 31** Remembering Ian Henderson

**Become a contributor...** Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Spring 2020 issue: **3 January 2020**.

Front cover image ©Shutterstock



We wish all our readers a very merry  
Christmas and happy new year



## WELCOMING YOUR NEW PRESIDENT

Professor Raj Thakker took over as President of the Society at the AGM during the Society for Endocrinology BES conference 2019. Raj is the May Professor of Medicine at the University of Oxford and a former Endocrine Network convener for the Society. We look forward to learning about his plans and aspirations for the Society, which you will be able to read about in the next issue.



Raj Thakker

## WITH GRATEFUL THANKS

Our thanks are due to Graham Williams (London) for all his hard work and dedication as Society President from 2016 to 2019. Among his main priorities as President were to ensure that the Society caters for every member and is prepared for the future.

This led to the introduction of the

Leadership and Development Awards Programme, to support and develop upcoming leaders. This exciting initiative will shape the Society for many years to come.

We also thank our retiring Council members, Ruth Andrew (Edinburgh), Mark Gurnell (Cambridge) and Martin Hewison (Birmingham), for their contributions and input to the Society.

We welcome new Council members Shareen Forbes (Edinburgh), Marie Freel (Glasgow) and Tara Kearney (Manchester), as well as all our new committee chairs and members who will start their roles in January 2020.

## SOCIETY JOURNAL UPDATE

*Journal of Endocrinology* and *Journal of Molecular Endocrinology* are pleased to announce that Professor Martin Haluzik (Prague, Czech Republic) will be joining Colin Farquharson (Edinburgh) as the journals' latest co-Editor-in-Chief at the start of 2020.

We would also like to say a huge thank you to Sof Andrikopoulos (Melbourne, Australia) as he ends his term of office. Dr Andrikopoulos has done fantastic work for both journals over the years and we wish him all the best in the future.



## SHARE AND ENHANCE YOUR CLINICAL EXPERTISE

National Clinical Cases 2020 is taking place on Thursday 12 March at the Royal Society of Medicine, London. It will showcase ten oral communications from the highest-scoring submitted cases, and provide an ideal forum for trainees to present clinical cases to peers and established endocrinologists. Find out more and register at [www.endocrinology.org/events/clinical-cases/national-clinical-cases-2020](http://www.endocrinology.org/events/clinical-cases/national-clinical-cases-2020).

## HELP IMPROVE MEDIA REPORTING

Become a Society Media Ambassador and share your expertise to help improve science and health reporting in the media. Media Ambassadors work alongside the Society's Press Office to provide accurate and responsible media reporting of endocrinology-related topics. Find out more in our free guide at [www.endocrinology.org/outreach/public-engagement/opportunities/engaging-with-the-media](http://www.endocrinology.org/outreach/public-engagement/opportunities/engaging-with-the-media).

## DON'T MISS THE SOCIETY'S LATEST BLOG POSTS

Visit The Endocrine Post at [www.endocrinologyblog.org](http://www.endocrinologyblog.org) for interviews with leading endocrinologists, who presented at SIE BES 2019.



Martin Haluzik



Colin Farquharson

## WITH REGRET

We are sorry to announce the death of Nurse Member, Nikki (Veronica) Kieffer.

Nikki was a key part of the Society in so many ways. She had been Chair of the Nurse Committee, led the development and publication of the *Competency Framework for Adult Endocrine Nursing*, championed the creation of the Society for Endocrinology-Oxford Brookes Masters-level module in Endocrine Nursing and was the inaugural winner of our Endocrine Nurse Award. A full obituary will appear in the next issue of *The Endocrinologist*.



Nikki Kieffer

## ATTRACT THE BEST TALENT

We can highlight your job vacancies to members, and help you attract the best candidates from the endocrine community. Email your job adverts to [media@endocrinology.org](mailto:media@endocrinology.org) and view current vacancies at [www.endocrinology.org/careers/jobs](http://www.endocrinology.org/careers/jobs).



## SOCIETY CALENDAR

12 March 2020  
**NATIONAL CLINICAL  
CASES**  
London, UK

**ENDOCRINE ACADEMY:**  
20-22 April 2020  
**CLINICAL UPDATE**  
Birmingham, UK  
20-21 April 2020  
**ENDOCRINE NURSE  
UPDATE**  
Birmingham, UK  
21-22 April 2020  
**CAREER DEVELOPMENT  
WORKSHOP**  
Birmingham, UK

16-18 November 2020  
**SfE BES 2020**  
Harrogate, UK

[www.endocrinology.org/  
events](http://www.endocrinology.org/events) for full details



## GRANT AND PRIZE DEADLINES

11 March 2020  
**TRAVEL GRANTS**  
18 March 2020  
**PATIENT SUPPORT  
GROUP GRANTS**  
18 March 2020  
**SUMMER STUDENTSHIPS**  
25 March 2020  
**PUBLIC ENGAGEMENT  
GRANTS**  
31 March 2020  
**JOURNAL OF  
MOLECULAR  
ENDOCRINOLOGY  
COMIC STRIP  
COMPETITION ENTRIES**  
8 April 2020  
**REGIONAL CLINICAL  
CASES GRANTS**  
8 April 2020  
**PRACTICAL SKILLS  
GRANTS**

[www.endocrinology.org/  
grants](http://www.endocrinology.org/grants) for full details of all  
Society grants and prizes

## SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, [www.endocrinology.org](http://www.endocrinology.org). *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access and free to all.



### JOURNAL OF ENDOCRINOLOGY

#### Central GH signalling is not required for pubertal timing

The growth hormone (GH) receptor is expressed in several regions of the brain, including leptin receptor- and kisspeptin-expressing hypothalamic neurones, which are important in regulating puberty and fertility. Bohlen *et al.* hypothesised that GH might play a role in regulating the hypothalamic-pituitary-gonadal (HPG) axis and the onset of puberty.

They ablated GH receptor in the whole brain, or in kisspeptin-expressing or leptin receptor-expressing neurones. While GH signalling in specific neural populations can potentially modulate hypothalamic gene expression related to

the reproductive system or indirectly contribute to the progression of puberty, GH action in kisspeptin cells or in the entire brain was not required for sexual maturation. Receptor ablation in leptin receptor-expressing cells delayed puberty progression, reduced serum leptin levels, decreased body weight gain and compromised the ovulatory cycle in some individuals, while the lack of GH effects in the entire brain prompted shorter oestrous cycles.

These findings suggest that GH can modulate brain components of the HPG axis, although central GH signalling is not required for the timing of puberty.

Read the full article in *Journal of Endocrinology* **243** 161–173

### JOURNAL OF MOLECULAR ENDOCRINOLOGY

#### Genetics and the timing of puberty

Delayed puberty is a common presentation in paediatric endocrinology which results from many different pathological mechanisms. Pubertal timing is known to be heritable; in the majority of patients presenting with delayed puberty, there is a clear family history of delayed or disturbed puberty. Thus, genetic factors play a key role in determining its timing.

Sasha Howard has reviewed the causal genetic defects associated with disrupted puberty. Genome-wide association studies and next generation sequencing have identified many different genes that associate with pubertal timing, as well as gene defects that lead to delayed puberty. The review highlights key roles for

genes that control (a) the development of the gonadotrophin-releasing system during fetal development, (b) the balance of inhibitory and excitatory signals that act upstream of gonadotrophin-releasing hormone secretion, and (c) energy homeostasis and metabolic balance.

These genetic insights have increased understanding of the pathogenesis of disrupted puberty and have future translational potential for the diagnosis and treatment of pubertal disorders.

Read the full article in *Journal of Molecular Endocrinology* **63** R37–R49

You can also read a feature article by Dr Howard on page 6 of this issue.

### ENDOCRINE-RELATED CANCER

#### The genetics of male breast cancer

Male breast cancer (MBC) is very rare and accounts for <1% of all breast cancers. Compared with female breast cancer, MBC has been poorly characterised at the molecular level. Clinical management of MBC is currently guided by our greater understanding of the disease in females, but whether MBC is a distinct disease is not known.

Moelans *et al.* obtained DNA from 45 formalin-fixed paraffin-embedded (FFPE) MBCs with matched normal tissues, as well as 90 unmatched MBCs (52 FFPE, 38 fresh-frozen). DNA was subjected to massively parallel sequencing, targeting all exons of 1943 cancer-related genes. Mutations and copy number alterations were compared with publicly available female breast cancer data.

The genomic landscape of MBC shared similarities with female disease, with common somatic mutations in *PIK3CA* and *GATA3* and 40% of the most frequently amplified genes overlapping between the sexes. Somatic mutations in genes regulating chromatin function and homologous recombination deficiency-related signatures were more prevalent in MBC. Amplifications in *MDM2* were more frequent in MBC than in female disease and this correlated with protein expression and predicted poor outcome.

MBC shares similarities with female breast cancer, but clear differences exist that should be accounted for in the classification and management of this disease.

Read the full article in *Endocrine-Related Cancer* **26** 779–794

### ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.



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#### Oestradiol improves biological rhythms in a rat menopause model

The perimenopausal transition is often associated with hot flushes, sleep disruption, metabolic changes and other symptoms. The mechanisms are incompletely understood, but both ageing and a loss of ovarian oestrogens play contributing roles. The timing and length of oestradiol treatment pose key clinical questions in the management of symptoms.

Yin *et al.* explored the effect of timing of oestradiol interventions in curtailing menopausal symptoms. Using a rat model of mechanically induced menopause, induced in either reproductively mature (4-month-old) or ageing (11-month-old) female rats, they investigated the effect of oestradiol supplementation for differing lengths of time on the diurnal rhythms of activity, food intake, core body temperature and body weight of the animals.

Oestradiol supplementation promoted the stability of core body temperature, food intake and weight gain, and locomotor activities. Moreover, oestradiol supplementation reversed the effects of ageing overall, even when the animals' treatment was delayed.

Read the full article in *Neurobiology of Aging* **83** 1–10

## CLINICAL ENDOCRINOLOGY

### Bone density in adolescents with cerebral palsy

Cerebral palsy is the most common motor disorder amongst children. Many children and young adults with cerebral palsy have reduced mobility, nutritional deficiencies, low sex hormones and take anti-convulsant medication, all of which lead towards poor bone health.

Trinh *et al.* assessed changes in bone mineral density (BMD) in a retrospective longitudinal study over a 12-year period in 45 young people, 16 of whom had five dual-energy X-ray absorptiometry scans. Bone density was low in childhood, with all first-measured BMD Z-scores being less than -2.0. There was an increase in BMD through puberty (mean 4–8%) and bone density was

maintained in early adulthood, suggesting a deficit in bone accrual rather than loss of BMD. 25% of patients received bisphosphonate, with no effect, and there was inconsistent use of sex steroids. The authors suggest improving muscle strength, nutrition and mobility is important to optimise bone health, although they also comment that the cohort was not large enough to demonstrate that increases in weight-bearing exercise improved BMD.

Attention to bone health in childhood is important for a population at risk of a low BMD. More work is needed to understand how BMD can be improved further.

Read the full article in *Clinical Endocrinology* **91** 517–524

## ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

### Prolonged acidosis in SGLT2i-induced euglycaemic diabetic ketoacidosis

Sodium glucose-like transporter-2 inhibitor (SGLT2i) drugs are widely prescribed in type 2 diabetes (T2DM). They inhibit glucose reabsorption, inducing glycosuria. They also induce euglycaemic diabetic ketoacidosis (EDKA) at a rate of 0.1%, the mechanism for which is unclear.

Rafey *et al.* describe two patients with T2DM who developed EDKA on SGLT2i post-operatively. They required 92 hours of treatment compared with a mean 35 hours in DKA in T1DM. Potential mechanisms include impairment by SGLT2i of ketone excretion (unlikely as both patients had marked ketonuria) or complete  $\beta$ -cell failure (although one patient was on basal bolus insulin as well as

SGLT2i). SGLT2i stimulates  $\alpha$ -cell glucagon production which decreases insulin, suggesting a mechanism for insulin deficiency. Both patients had undergone surgery, which itself causes reduced insulin sensitivity and may have contributed. The authors suggest stopping SGLT2i 48 hours before surgery. In addition, low dose insulin infusion was used, and maybe a higher dose of insulin could be considered, with glucose infusion, to inhibit ketogenesis.

More detailed mechanistic information is needed, including insulin, glucagon, urine and blood ketones throughout an episode of EDKA, to achieve a greater understanding of the mechanism of this rare but serious complication of SGLT2i use.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 19-0087

## ENDOCRINE CONNECTIONS

### Ovarian FSH resistance

Primary ovarian insufficiency (POI) can be caused by mutations in the follicle-stimulating hormone (FSH) receptor, which leads to FSH-resistant ovaries (FSHRO). Women with this single-gene form of POI tend to have high gonadotrophin levels, normal levels of anti-Müllerian hormone and shorter height (compared with women with other forms of POI).

Luiro *et al.* set about characterising longer term health outcomes in a small Finnish cohort of women with FSHRO, using data from the national FINRISK population cohort as controls. They found that FSHRO was associated with reduced bone density despite oestrogen replacement, but not with increased

cardiometabolic risk (although a more android distribution of body fat was observed). More than half of the cohort had small streak ovaries on examination, with only a small number showing antral follicles. However, oocyte donation resulted in successful pregnancies for the majority of women. The team also found that depression and sexual dysfunction were more commonly reported in the FSHRO cohort compared with controls.

They concluded that earlier initiation of hormone replacement therapy might be beneficial in women with FSHRO, and that their healthcare professionals should remember the need to address psychological and sexual well-being.

Read the full article in *Endocrine Connections* **8** 1354–1362

### Synapses' role in the need to sleep

We all experience the need to sleep (sleep pressure), but the underlying mechanisms present challenging questions. Sleep pressure is influenced by how long we have been awake, how active we have been, and our intrinsic body clock. Twin papers highlight the importance of these influences by studying what happens at mouse forebrain synapses over the 24-hour cycle and under conditions of sleep deprivation.

Noya *et al.* have shown that gene expression at synapses shows strong circadian rhythmicity, and that this depends upon a functional molecular clock (rhythmicity is not seen in mice lacking the core clock gene *Bmal1*). Abundance of synaptic proteins correlates with mRNA transcripts under normal conditions, but this protein rhythmicity is lost under conditions of sleep deprivation, whilst mRNA transcript rhythmicity is not.

Brüning *et al.* looked at phosphoprotein rhythms at the synapse across the circadian cycle and following sleep deprivation. Protein phosphorylation indicates a change in protein function, and so this study highlights which biological processes at the synapse might be rhythmic. Like the first paper, this article reports large-amplitude circadian rhythms in synaptic phosphoprotein abundance, which are abolished by sleep deprivation.

Together, these studies suggest that transcriptional control at the synapse is probably conferred by the circadian clock, but translation and protein phosphorylation are regulated by patterns in activity and rest. Thus, gene expression arguably keeps track of time of day, whilst protein expression and phosphorylation track sleep pressure.

Read the full articles in *Science* **366** doi:10.1126/science.aav2642 and doi:10.1126/science.aav3617, as well as a commentary at doi:10.1126/science.aay5304



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# TIMING OF PUBERTY: WHY IS IT CHANGING AND WHY DOES IT MATTER?

WRITTEN BY SASHA HOWARD



Puberty is the key developmental stage of transition from childhood to adult life, with the achievement of adult height and body proportions, the development of external sexual characteristics and the capacity to reproduce.

In some children, puberty may take place prematurely to produce precocious puberty, whilst, in others, it fails to be switched on at the appropriate time, leading to delayed puberty. The mechanisms behind these pubertal timing abnormalities are varied, and many remain incompletely understood.

## THE PROCESS OF PUBERTY

Central to the process of puberty, and heralding its onset, is upregulation of pulsatile gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus. This, in turn, results in increased luteinising hormone (LH) and follicle-stimulating hormone release from the anterior pituitary, which promotes gonadal maturation, gametogenesis and sex steroid and peptide hormone production.

The hypothalamic-pituitary-gonadal (HPG) axis is active at three main developmental stages. The axis develops during fetal life, is reactivated in the postnatal period during 'mini-puberty', and then stays quiescent from 2 years of age until around 8–9 years, with minimally detectable LH concentrations. At puberty, a co-ordinated array of signals allows the reactivation of the axis after this mid-childhood period of dormancy. It is still unclear which primary mechanisms suppress the axis after mini-puberty and allow the release of this 'puberty brake' at the end of mid-childhood.<sup>1</sup>

## A SPECTRUM OF TIMING

There is a spectrum of pubertal timing in the general population, with a mean onset of Tanner genital stage 2 (G2) at 11.5 years in boys and Tanner breast stage 2 (B2) at 11 years in girls (Figure). Whilst the norms for pubertal onset do vary between ethnic groups, the age limits observed for G2 in boys are 9–14 years, and for B2 in girls are 8–13 years.

However, the timing of puberty in most countries in the developed world exhibited a shift to earlier onset in the first half of the 20th century, most notably in girls.<sup>2</sup> More recently, there has been an increasing trend towards an earlier age at pubertal onset (B2 or G2), but also towards a larger number of children completing their puberty at a later age.<sup>3</sup>

## FACTORS INVOLVED

Nutritional status, adoption, geographical migration and emotional well-being all have an effect on pubertal timing. Nutritional changes clearly have a key role, as shown by the positive correlation between age at puberty onset and childhood body size, particularly in girls. These trends are less apparent in boys.<sup>4</sup>

The relationship between fat mass and puberty is mediated, at least in part, through the permissive actions of leptin, a key regulator of body mass which is produced from white adipose tissue. However, ghrelin, neuropeptide Y and many other signalling pathways are likely to be important in the nutritional control of pubertal timing.

The effect of possible endocrine-disrupting chemicals (EDCs) on the timing of puberty has also been an ongoing concern.<sup>5</sup> Many compounds, including polybrominated biphenyls, bisphenol A, herbicides and phthalates, have

been implicated as potential EDCs, responsible for contributing to this observed trend.

Despite the importance of environmental factors, a genetic influence on the timing of puberty is fundamental. Although the timing of pubertal onset varies within and between different populations, it is a highly heritable trait, as shown by the high correlation of the timing of sexual maturation within families and in twin studies. Previous epidemiological studies and genetic approaches estimate that 50–80% of the variation in pubertal onset is under genetic control.<sup>6</sup> Despite this strong heritability, little is known about the control mechanisms.

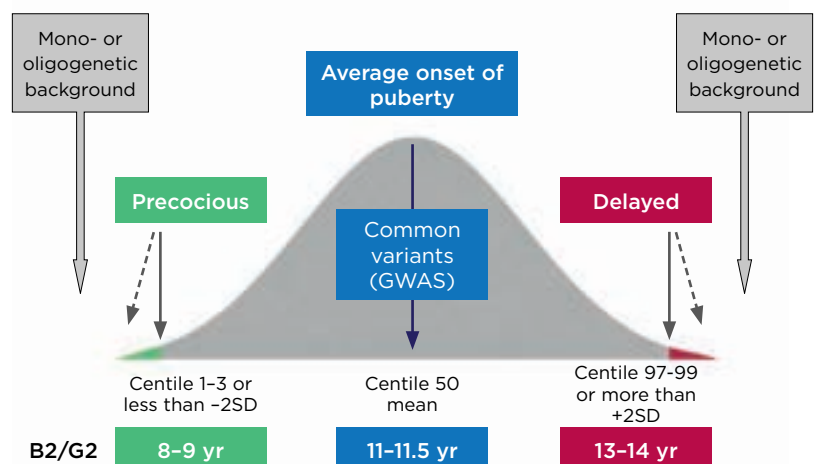
## UNDERSTANDING GENETIC CONTROL

Attempts to identify key genetic regulators have ranged from genome-wide association studies of age-at-menarche, examining pubertal timing in healthy women, to next generation sequencing approaches to identify causal mutations in disease cohorts with delayed, absent or precocious puberty. The existence of genetic heterogeneity is supported by several large genome-wide association studies, with nearly 400 loci associated with timing of menarche to date, explaining approximately 7.4% of the population variance.<sup>7</sup>

Advances in our understanding of the genetic control of the HPG axis via mono- and digenic pubertal disorders have come both from patients with late or absent puberty (cohorts of isolated pubertal delay or hypogonadotropic hypogonadism), and also from familial central precocious puberty (CPP).

Mutations in the pubertal brake gene *MKRN3*,<sup>8</sup> and more rarely in the kisspeptin gene *KTSS1* and *DLK1*, highlight the importance of upstream control of GnRH secretion in the pathogenesis of CPP. In delayed or absent puberty, more than 40 genes have been identified, mutation of

**Figure.** The spectrum of pubertal timing in the general population, with a mean onset of Tanner genital stage 2 (G2) at 11.5 years in boys and Tanner breast stage 2 (B2) at 11 years in girls. The norms for pubertal onset vary between ethnic groups, but the age limits observed for G2 in boys are 9–14 years, and for B2 in girls are 8–13 years. GWAS, genome-wide association studies. ©S Howard



which causes or contributes to the aetiology of these conditions. Many of these are specific to isolated delayed puberty, syndromic pubertal delay or hypogonadotropic hypogonadism.<sup>1</sup>

These genetic causes demonstrate that defects in GnRH neuronal development, GnRH secretion, upstream control or downstream action may all cause disorders of pubertal timing.

*'50–80% of the variation in pubertal onset is under genetic control. Despite this strong heritability, little is known about the control mechanisms.'*

#### CLINICAL IMPACT

Disturbances of puberty encompass an important group of pathologies within the field of paediatric endocrinology, affecting over 4% of adolescents. In addition, abnormal timing of pubertal development is associated with adverse health and psychosocial outcomes. This is not only important to the individual, but also has a potential major impact on public health, especially in view of the secular trend towards an earlier age of puberty onset.

Early puberty, in particular, is associated with adverse health outcomes, including breast and endometrial cancer, obesity, type 2 diabetes, cardiovascular disease, short stature and even increased mortality. Until recently, it had not been clearly shown that late pubertal timing

is also associated with adverse health outcomes, but data from the UK Biobank study from both genders have demonstrated that delayed puberty also has profound impacts on health in later life.<sup>9</sup>

The considerable progress in understanding the mechanisms which control puberty over the last 10 years has been a success story for basic research in neuroendocrinology, but has also been translated into clinical practice to allow a better understanding of the mechanisms of disordered pubertal development and, in some cases, to enable diagnostic genetic testing and counselling.

#### SASHA HOWARD

NIHR Academic Clinical Lecturer in Paediatric Endocrinology, Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

#### REFERENCES

1. Howard SR & Dunkel L 2019 *Endocrine Reviews* **40** 1285–1317.
2. Parent AS *et al.* 2003 *Endocrine Reviews* **24** 668–693.
3. Parent AS *et al.* 2015 *Frontiers in Neuroendocrinology* **38** 12–36.
4. Sorensen K *et al.* 2010 *Journal of Clinical Endocrinology & Metabolism* **95** 263–270.
5. Mouritsen A *et al.* 2010 *International Journal of Andrology* **33** 346–359.
6. Morris DH *et al.* 2011 *Paediatric & Perinatal Epidemiology* **25** 306–311.
7. Day FR *et al.* 2017 *Nature Genetics* **49** 834–841.
8. Simon D *et al.* 2016 *European Journal of Endocrinology* **174** 1–8.
9. Day FR *et al.* 2015 *Scientific Reports* **5** 11208.

## THE RHYTHMS OF LIFE: THE IMPORTANCE OF GLUCOCORTICOID PULSATILITY

WRITTEN BY THOMAS UPTON



Rhythms characterise all living things, from the type of content we post on Twitter,<sup>1</sup> to the metabolism of individual cells in every part of our bodies.<sup>2</sup>

Rhythms that oscillate over days, weeks or longer, such as the human menstrual cycle, are termed 'infradian'.

'Circadian' rhythms have an intrinsic period close to 24 hours. The sleep hormone melatonin is circadian. Its rhythm persists despite the absence of external environmental cues and is therefore a useful marker of circadian phase.

'Diurnal' rhythms describe patterns of activity that mainly occur in the daytime: thus a diurnal rhythm may or may not also be circadian. Daily physical activity is an example of a diurnal rhythm in most people.

Rhythms that occur with a period of less than 24 hours are 'ultradian', and may be as short as a few minutes – as in the case of insulin secretion.

Cortisol, the glucocorticoid hormone that is vital for both survival and the acute stress response, shows a diurnal circadian rhythm and superimposed ultradian rhythm in humans.<sup>3</sup> Pulsatile secretion of cortisol occurs approximately every 90 minutes and can be observed in healthy people when blood sampling is frequent enough.<sup>4</sup> In fact, cortisol pulsatility persists even in pathological states, such as Cushing's, caused by adrenocorticotrophin-secreting pituitary tumours.<sup>5</sup>

#### WHAT CAUSES THE GLUCOCORTICOID ULTRADIAN RHYTHM?

Previously, it was considered that a pulse generator must exist in the hypothalamus to account for these rapid oscillations. However, while lesions to the master clock in the suprachiasmatic nucleus abolish circadian rhythms in rodents, they do not disrupt cortisol pulsatility,<sup>6</sup> which remains ultradian.

An alternative hypothesis is that cortisol pulsatility is itself an intrinsic property of the hypothalamic-pituitary axis. Mathematical modelling predicts that ultradian secretion of cortisol is due to the dynamic interaction between positive 'feed-forward' from the hypothalamus

and pituitary, and negative feedback from cortisol produced by the adrenal gland.<sup>7</sup> This theory has been supported by rodent experiments where ultradian oscillations of cortisol continue in spite of constant corticotrophin-releasing hormone infusion.<sup>8</sup> Rapid negative feedback by glucocorticoid inhibition must be the key factor that regulates the dynamic ultradian rhythm.

### ARE ULTRADIAN RHYTHMS IMPORTANT?

As we have seen, the rhythm of glucocorticoids is highly dynamic. Early in the morning, there is a circadian rise in cortisol that anticipates waking and prepares the individual for the challenges of the day. However, the hormone doesn't then simply decline smoothly over the day; secretion continues in burst-like pulses that decrease in amplitude until the nadir is reached overnight.

Recognising that the glucocorticoid rhythm is complex should help clinicians and others to understand why single time-point measurements of cortisol are difficult or impossible to interpret, why the healthy normal range for morning cortisol is so broad, and why normal variation can frequently overlap with pathological states such as Cushing's syndrome.

*'New treatment approaches that consider the importance of ultradian, as well as circadian, variation are now emerging as potential new tools for endocrinologists in clinical practice.'*

Evidence that the ultradian rhythm of cortisol is metabolically important comes from animal and tissue experiments, and more recently in humans. Pulsatile compared with continuous exposure to glucocorticoids alters the expression of genes in many tissues, including the liver and brain.<sup>9</sup> Furthermore, in adrenalectomised rats, the response to stress was blunted when cortisol was replaced continuously rather than in a pulsatile manner.<sup>10</sup>

Recent work by PhD student Ben Flynn (University of Bristol) has shown that binding of the glucocorticoid receptor to DNA is dynamically synchronised with pulsatile signals of cortisol. In contrast, when there is continuous exposure to cortisol, transcription of glucocorticoid receptor-dependent genetic targets involved in metabolic regulation is significantly altered.

### STUDIES IN HUMANS

Evidence of the physiological relevance of glucocorticoid pulsatility in humans has thus far not been well described and is a clear area for future research.

One hypothesis is that the poorer quality of life and health outcomes commonly reported in patients with Addison's disease<sup>11</sup> could at least partly be attributed to the lack of endogenous glucocorticoid pulsatility as well as non-physiological replacement dosing. In a study of healthy volunteers, cortisol was suppressed using metyrapone. Participants then received hydrocortisone, either by means of standard oral doses, via smooth 'circadian' subcutaneous infusion, or as a series of ultradian subcutaneous pulses. The same total dose of hydrocortisone was

given in all three settings. The ultradian replacement was associated with better self-reported sleep quality, better working memory and differential connectivity in brain regions important for emotional processing.<sup>12</sup>

The PULSES trial ([www.isrctn.com/ISRCTN67193733](http://www.isrctn.com/ISRCTN67193733)) aimed to explore this through the novel use of subcutaneous pulsatile glucocorticoid replacement, compared with standard oral doses, in patients with Addison's and congenital adrenal hyperplasia. Preliminary results presented at the recent Society for Endocrinology BES conference in Brighton indicate that as in healthy volunteers, the pattern of glucocorticoid replacement is extremely important for normal cognitive function.

Better understanding of the dynamics of adrenal hormones should also contribute to improvements in endocrine diagnosis and treatment. The ULTRADIAN Dynamic Hormone Diagnostics multicentre trial ([www.ultradian.eu](http://www.ultradian.eu)) is currently recruiting both healthy volunteers and patients with endocrine diseases. In this study, healthy adrenal steroid dynamics measured using novel, non-invasive ambulatory sampling technology are compared with the dynamics of endocrine diseases such as Cushing's, Addison's and primary aldosteronism. By measuring hormones repeatedly over 24 hours, far more information can be gathered about both healthy normal variation and pathological hormone states. This information will then be integrated using mathematical algorithms and machine-learning techniques to reduce diagnostic time and make management decisions more personal to each patient.

### IN SUMMARY

Our lives are rhythmic on scales that range from months to minutes. Each rhythm is important and, together, they create an environment of dynamic equilibrium.

When it comes to the clinic, understanding that single, integrated or limited time-point measurements may be inaccurate or misleading is essential. Likewise, being mindful that many of our treatments do not mimic physiological rhythmicity may be extremely important for patient well-being. New treatment approaches that consider the importance of ultradian, as well as circadian, variation are now emerging as potential new tools for endocrinologists in clinical practice.

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### REFERENCES

1. Dzogang F *et al.* 2018 *PLoS One* **13** doi: 10.1371/journal.pone.0197002.
2. Eckel-Mahan K & Sassone-Corsi P 2013 *Physiological Reviews* **93** 107–135.
3. Veldhuis JD *et al.* 1989 *American Journal of Physiology* **257** E6–E14.
4. Henley DE *et al.* 2009 *Journal of Medical Engineering & Technology* **33** 199–208.
5. Roelfsema F *et al.* 2014 *Journal of Clinical Endocrinology & Metabolism* **99** 3836–3844.
6. Wait, EJ *et al.* 2012 *European Journal of Neuroscience* **36** 3142–3150.
7. Walker JJ *et al.* 2010 *Proceedings of the Royal Society B* **277** 1627–1633.
8. Walker JJ *et al.* 2012 *PLoS Biology* **10** e1001341.
9. Stavreva DA *et al.* 2009 *Nature Cell Biology* **11** 1093–1102.
10. Sarabdjitsingh RA *et al.* 2010 *Endocrinology* **151** 5369–5379.
11. Bensing S *et al.* 2016 *European Journal of Endocrinology* **175** R107–R116.
12. Kalafatakis K *et al.* 2018 *Proceedings of the National Academy of Sciences of the USA* **115** E4091–E4100.





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# REPRODUCTIVE MEDICINE: TIME IS OF THE ESSENCE

WRITTEN BY KUGAJEEVAN VIGNESWARAN & SESH KAMAL SUNKARA



In the field of reproductive medicine, the concept of timing is of paramount importance. Indeed, the majority of consultations that take place between a reproductive medicine specialist and a patient will include some mention of time and its implications for treatment and outcomes.

As well as examining some of these time-related concepts, this overview will consider the challenges faced by healthcare professionals working in the care of infertility.

## FERTILITY AND AGEING

One peculiarity of the human ovary is the cessation of activity at the age of menopause, a demise of function which is not seen in the testes. The total pool of functional follicles within the ovaries, having been formed by the 20th week of fetal life, continues to undergo depletion through successive waves of follicular growth and atresia, until final exhaustion.<sup>1</sup>

This loss is exponential, with initial numbers estimated at 6–7 million oocytes declining to 500,000 by puberty. In fact, during a female's entire reproductive lifespan, only around 400 oocytes are capable of ovulation.<sup>1</sup>

Fertility declines with age across all populations in both men and women. However, the effects are more pronounced in women. It has been shown that, for women, the chance of conception decreases significantly after the age of 35 years.<sup>2</sup>

Although sperm parameters in men can begin to show a decline from the age of 35, population studies have shown that fertility per se does not appear to lessen before approximately 50 years. At the age of 50–54, fertility rates were found to be 73% of those of men in their early 20s.<sup>3</sup>

## IMPACT ON FERTILITY TREATMENT

The impact of ageing on fertility treatment outcomes is quite evident when referring to birth rate outcome registries. When examining Human Fertilisation and Embryology Authority data for 2017 birth rates for all women having *in vitro* fertilisation (IVF) in the UK, one can observe a clear trend. Comparing fresh IVF cycles only, the birth rate is 30% in the under-35 age group per embryo transfer, 23% for those aged 35–37, 15% for the 38–39 age group and as low as 4% for women aged 43–44.<sup>4</sup>

A similar pattern is seen in IVF treatment cycles performed in the USA. The organisation responsible for reporting outcomes, the Society for Assisted Reproductive Technology, stated in 2017 that there was a 40.5% singleton live birth per cycle started for under 35s, dropping to 30.3% in the 35–37 age group, 18.7% in those aged 38–40, and as low as 9.1% for women aged 41–42.<sup>5</sup>

This age-related decline in fertility should be considered when deciding when one should begin assessment for couples. As infertility can be defined as the failure to conceive after 1 year of unprotected vaginal sexual intercourse or exposure to sperm,<sup>6</sup> early clinical assessment can be considered after 6 months without conception for women aged over 35, as per NICE guidelines.<sup>7</sup>

## INEFFICIENCY OF HUMAN CONCEPTION

Even in the most optimal conditions, the chance of human conception is no more than 30–40% within each menstrual cycle.<sup>8</sup> In the general population (which covers all ages and includes people with fertility

problems), it is estimated that 84% of women would conceive within 1 year of regular unprotected sexual intercourse. This rises cumulatively to 92% after 2 years and 93% after 3 years.<sup>9</sup>

For conception to be possible, intercourse must take place at a time when both the oocyte and the sperm are at maximal viability. This 'fertile window' has traditionally been considered to be the 6-day interval ending on the day of ovulation. This window can be ascertained by analysing the intermenstrual interval, using urinary ovulation predictor kits to look for the luteinising hormone (LH) surge or monitoring changes in body temperature or cervical mucus.

Data have consistently shown that peak fecundability (the probability of pregnancy per month) occurred if intercourse took place within the 3-day interval ending on the day of ovulation.<sup>10</sup>

*'Even in the most optimal conditions, the chance of human conception is no more than 30–40% within each menstrual cycle.'*

One particular study of women who self-reported their menstrual cycles to be generally 'regular' showed that the likelihood of conception increased during this fertile 3-day window. (These women responded 'yes' to the question 'Is the length of time between your periods about the same each cycle and therefore regarded as regular?') The probability of clinical pregnancy increased from 2% on cycle day 7 to 9% on cycle day 13 and decreased to less than 2% by cycle day 21.<sup>11</sup>

Cycle fecundability also increases with the frequency of intercourse during the fertile window.<sup>12</sup> A retrospective study, which analysed almost 10,000 semen specimens, demonstrated that semen quality, sperm concentrations and motility remained normal even with daily ejaculation, putting to rest the common misconception held that frequent ejaculations reduce male fertility. Furthermore, prolonged abstinence intervals of 5 days or more can adversely affect sperm parameters.<sup>13</sup>

## MONITORING OVULATION

The timing of peak fertility can vary significantly, even in women having regular cycles. Predicting ovulation can be frustrating for couples attempting conception, and there is no substantial evidence<sup>14</sup> that monitoring by any of the purported methods can increase fecundability. Applying technology in the form of tracking applications has gained popularity over the years. However, relying solely on these tools to time intercourse should be exercised with caution. A recent study using data collected from such applications revealed some interesting insights into ovarian cycle physiology. The authors analysed key characteristics from

more than 600,000 menstrual cycles. The results revealed significant variability in cycle and follicular phase lengths.<sup>15</sup>

Determination of ovulation by the app was achieved retrospectively using an algorithm based on basal body temperatures, menstrual cycle parameters and positive LH tests.

*'Understanding the time-critical nature of human conception underpins the creation of the protocols that are used in assisted reproductive technology.'*

An LH surge results in triggering a follicle to rupture. The surge begins approximately 28–48 hours before follicle rupture, and peak LH levels are noted at 12 hours prior to rupture. Corpus luteum formation follows follicular rupture, and progesterone secretion begins. The thermogenic effect of progesterone results in a distinct rise of 0.2–0.3°C following ovulation, allowing basal body temperatures to be used as a marker for the luteal phase of the menstrual cycle.<sup>16</sup>

The data demonstrated that cycle length differences were noted primarily as a result of a variable follicular phase. The mean follicular phase length was 16.9 days. The authors concluded that cycle length alone may not suffice to identify the fertile window, and tracking supplemental physiological parameters is imperative.

One large study demonstrating this point showed that changes in cervical mucus, namely increased volumes of slippery and clear mucus, were able to predict a higher chance of conception as well as or better than basal body temperature or urinary LH monitoring.<sup>17</sup>

### THE IMPLANTATION WINDOW

Following fertilisation of an egg, the tiny embryo – positioned in the oviduct – has to undertake a journey of mammoth proportions. Upon reaching the uterus, the embryo engages in a complex interaction with the maternal interface. This two-way communication results in physical contact between the embryo and the endometrium and subsequent implantation.

Long range signalling to the pituitary-ovarian axis regarding the implanted embryo results in maintenance of the corpus luteum and a sustained progesterone environment.

During the mid-secretory phase of the menstrual cycle, rising progesterone levels lead to the creation of a nutritionally rich glandular support network for the embryo. The endometrium undergoes significant histological changes, signalling the opening of the implantation window.

The implanted embryo, now at the blastocyst stage, is able to establish its own circulation as well as provoking maternal circulatory changes.

This intricate process depends entirely on the time-dependent opening of a receptive phase in the cycle, known as the implantation window. For

an embryo to thrive, early development and transport to reach the uterus in time for this receptive window are paramount. Beyond this point, the uterus will resist any further attempts at attachment.

### TIMING IN ASSISTED REPRODUCTIVE TREATMENT

Understanding the time-critical nature of human conception underpins the creation of the protocols that are used in assisted reproductive technology.

This can range from tailoring the dose and duration of follicle-stimulating hormone administration in order to achieve the optimal number of oocytes for fertilisation, to the timing of an embryo transfer following adequate luteal phase support with progesterone in an IVF cycle. Successful outcomes depend on our ability to perform the steps of treatment within optimal time frames.

Often the fine margins that distinguish a successful IVF cycle from an unsuccessful one hinge on time. With our greater understanding of the implantation window, both in the context of natural conception as well as in the application of this knowledge to assisted conception cycles, the field of reproductive medicine has seen continuing strides towards greater success for our patients.

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### REFERENCES

1. Macklon NS & Fauser BC 1999 *Hormone Research in Paediatrics* **52** 161–170.
2. American College of Obstetricians and Gynecologists & American Society for Reproductive Medicine 2008 *Fertility & Sterility* **90** S154–S155.
3. Menken J *et al.* 1986 *Science* **233** 1389–1394.
4. HFEA 2019 *Fertility Treatment 2017: Trends and Figures* [www.hfea.gov.uk/media/2894/fertility-treatment-2017-trends-and-figures-may-2019.pdf](http://www.hfea.gov.uk/media/2894/fertility-treatment-2017-trends-and-figures-may-2019.pdf).
5. SART 2019 *National Summary Report Preliminary Data 2017* [www.sartcorsonline.com/rptCSR\\_PublicMultYear.aspx](http://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx).
6. Zegers-Hochschild F *et al.* 2009 *Human Reproduction* **24** 2683–2687.
7. NICE 2013 *Fertility Problems: Assessment and Treatment CG156* [www.nice.org.uk/guidance/cg156](http://www.nice.org.uk/guidance/cg156).
8. Taylor A 2003 *BMJ* **327** 434–436.
9. te Velde ER *et al.* 2000 *Lancet* **355** 1928–1929.
10. Wilcox AJ *et al.* 1995 *New England Journal of Medicine* **333** 1517–1521.
11. Wilcox AJ *et al.* 2001 *Contraception* **63** 211–215.
12. Stanford JB & Dunson DB 2007 *American Journal of Epidemiology* **165** 1088–1095.
13. Levitas E *et al.* 2005 *Fertility & Sterility* **83** 1680–1686.
14. Sievert LL & Dubois CA 2005 *American Journal of Human Biology* **17** 310–320.
15. Bull JR *et al.* 2019 *npj Digital Medicine* **2** 1–8.
16. Su HW *et al.* 2017 *Bioengineering & Translational Medicine* **2** 238–246.
17. Dunson DB *et al.* 2001 *Human Reproduction* **16** 2278–2282.

# CHRONOTHERAPEUTICS: PAST AND PRESENT

## (or 'WHAT TIME SHOULD I TAKE THIS, DOCTOR?')

WRITTEN BY DAVID RAY



In the clinic, we are blessed with a superb range of potent, safe drugs, with established mechanisms of action and indications. These new weapons against disease make current physicians 'masters of the universe', holding in their hands the power of life and death. But do we use this power wisely?

All life on Earth ticks in time to the solar cycle. As our planet rotates, we experience changes in ambient light and temperature, with attendant changes in threat level and food availability. Humans, with relatively poor nocturnal special senses, are best able to find food during the day and, having fed, need a protected shelter to avoid predation by night. These fundamental needs drive much of human biology, through a system of internal timing mechanisms: the circadian clock. Understanding how this ancient survival mechanism impacts upon disease susceptibility and treatment response is new – an exciting field termed chronotherapeutics.

### EXAMINING THE EVIDENCE

It has been known since the 1950s that the statin class of drugs acts on a target, HMG-CoA reductase, that is only expressed in the liver at night. Therefore, simvastatin is prescribed to be taken at night, and the timing instruction is in the product insert. However, many patients don't know, or forget, this timing information, and dose in the morning: conditions of use likely to yield no therapeutic benefit. It's one example, but one which is well worked out. What about others?

Human clinical trials data are freely available and, in many cases, it is possible to identify individual drug administration times. In this way, it is possible to conduct virtual trials comparing active drug administration at different times of the day. These virtual trials can be done quickly, and at low cost, as the analysis is entirely at the level of the data.

These important studies have revealed striking findings related to the pharmacokinetics of the drugs and the therapeutic responses. So, time of day differences in response are common. The drugs likely to be implicated tend to have short half-lives (<8 hours). The indications include inflammatory, metabolic, vascular and neurological diseases. The trial re-analyses are now all publicly available, and can be used by patients, professionals and healthcare organisations to compare current practice with the ideal, correct time!<sup>1</sup>

### DAMAGE LIMITATION

In addition to evidence linking timing to drug duration of action and efficacy, there has been interest in applying clock logic to address the therapeutic index of effective drugs with significant toxicity, for example chemotherapy.

Francis Levy has undertaken some pioneering work looking at chemotherapy responses of tumour tissue and host healthy tissue. He has identified the presence of windows of opportunity where host sensitivity is at its lowest, so offering the chance for higher dosing of the active agent to more effectively hit the cancer, while sparing the rest of the body.

This application of clock logic to cancer medicine relies on there being differences in the operation of the circadian clock in cancer cells, or differential coupling of the core clock to output pathways. The proof of principle studies are done, but the difficulty in application lies in

heterogeneity between patients in terms of endogenous clock phase, as well as heterogeneity within the tumours.

### THE PERSONAL CLOCK

The application of time as a new way to personalise medicine is attractive. However, people show differences in circadian phase, with some being early, and some late. We refer to these differences using avian analogies: larks and owls. In addition, chronotype changes by age and sex, and internal timing systems will synchronise with behaviour, so shift workers have shifted clocks.

What would be ideal would be a simple way to determine a person's circadian phase, so that a drug can be timed to that individual's internal clock, and not the clock on the wall.

*'If 40% of drug targets oscillate under circadian control, a potential and avoidable cause of clinical failure is the mismatch between administration time and the peak expression of the drug target.'*

Currently, the gold standard is to take frequent blood samples, in dim light through the evening, to measure the rise in melatonin, the brain hormone needed for sleep. This dim-light melatonin onset (DLMO) is a research tool, and totally unsuited to clinical application.

To get round this log jam, a number of investigators are working on a simple, single blood test, to measure a biomarker of clock phase. Multiple models are now described, and validated, with an error of approximately 2 hours compared with the DLMO. Therefore, it is now possible to measure circadian phase in the clinic, and use that as the anchor point to time drug administration, e.g. '6 hours after the circadian peak of a core clock gene'.

### A JUSTIFIABLE EXPENSE

Drug development has a very high cost, with many promising compounds left as casualties by the road. Many of these molecules show engagement with the target, but fail in the clinic. If 40% of drug targets oscillate under circadian control, a potential and avoidable cause of clinical failure is the mismatch between administration time and the peak expression of the drug target. While comparing multiple times of day within a single trial greatly increases costs, there is a strong argument for considering time of day as a critical determinant of the study protocol.

So, what do we know? It's later than we think, but not too late to change. We can embrace the new biology of the circadian clock to enhance diagnostics and therapeutics for widespread human benefit.

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### REFERENCE

1. Ruben MD *et al.* 2019 *Science* **365** 547–549.

## PARATHYROID SURGERY: TIMING IN PREGNANCY

WRITTEN BY AIMEE DI MARCO & FAUSTO PALAZZO

Primary hyperparathyroidism (pHPT) does not decrease fertility but is detrimental to the health of mother and fetus. It is therefore an unfortunate truism that the optimal timing for parathyroid surgery in pregnancy would be before the pregnancy had occurred.

All women with pHPT of reproductive age (defined by WHO as 15–49 years) meet the National Institute for Health Research/International Consensus criteria for parathyroidectomy and are therefore usually referred for surgery. Those with known multiple endocrine neoplasia type 1 are managed more conservatively, being advised to undertake family planning and undergo surgery when their biochemistry, symptoms or end-organ damage necessitate.

Pregnant women with pHPT present a clinical dilemma, due to the need to balance the risks of untreated pHPT to the fetus and mother against the risks of the treatment.

### HOW OFTEN DOES THIS OCCUR?

It is hard to get an accurate estimate of the scale of this problem. First, the diagnosis of pHPT is most commonly incidental; calcium is not routinely measured in healthy young women, during pregnancy, or even in recurrent miscarriage. Secondly, the symptoms of hypercalcaemia (i.e. nausea and vomiting, fatigue and other non-specific malaise) overlap with those of a 'normal' pregnancy, causing the diagnosis to be easily missed. However, the best estimate is that pHPT occurs in 1 in 2000 (0.05%) women of reproductive age.<sup>1</sup>

Surgical series have shown that 8–10.5% of all parathyroidectomies are undertaken in women of reproductive age (equating to around one quarter of all parathyroidectomies in women) and 1–1.25% during pregnancy.<sup>2,3</sup> Given that the number of women having their first pregnancy after 35 years of age increased ninefold between 1970 and 2012,<sup>4</sup> it is probable that pHPT in pregnancy will be encountered more in the future.

*'It is an unfortunate truism that the optimal timing for parathyroid surgery in pregnancy would be before the pregnancy had occurred.'*

### RISKS OF DISEASE VERSUS SURGERY

As well as pre-eclampsia and miscarriage, pHPT has been linked to intrauterine growth retardation, polyhydramnios and stillbirth. Neonatal hypoparathyroidism and hypocalcaemia may result and, if unrecognised, present with tetany or seizures. The risk of these complications is dependent upon the biochemical severity of the pregnant woman's pHPT, as demonstrated in at least one large surgical series.<sup>2</sup>

Safe, non-surgical control of hypercalcaemia is restricted to oral or intravenous hydration. The effects of calcitonin are short-lived, bisphosphonates are known to cross the placenta and be detrimental to fetal skeletal development, and the safety of cinacalcet is unknown and



worrisome, given the presence of its target – the calcium-sensing receptor – in many tissues including the kidney, bone, brain and breast.

Surgery is the only definitive cure for pHPT. Standard pre-operative imaging using ionising radiation (SestaMIBI scanning, 4DCT, etc.) is ill-advised in pregnancy and, even with high quality ultrasound by an experienced sonographer, most pregnant women will have unlocalised disease.<sup>3</sup> Thankfully, cure may still be achieved in 97% of patients with a bilateral neck exploration when undertaken by a high-volume parathyroid surgeon. Parathyroidectomy under local anaesthesia and sedation is feasible, but usually confined to localised disease. Thankfully, modern general anaesthetic agents are non-teratogenic, and so the pregnancy-specific risks from general anaesthesia are restricted to miscarriage or preterm delivery.

The overall background risk of miscarriage in pregnancy is approximately 15%, but is highest early in the first trimester, decreasing to below 5% in the second.<sup>5,6</sup> The risk attributable to anaesthesia in neck surgery has been reported as a number needed to harm of 356 to precipitate one stillbirth and 63 for one preterm delivery.<sup>7</sup>

Given the greater background miscarriage rate in the first trimester, the second trimester is universally accepted as the most favourable time to intervene, with the greatest benefit to the woman and fetus. However, there is no absolute cut-off, with a gradual decline in the background rate of miscarriage through the first and into the second trimester. Surgery in the third trimester can be performed, but with an increase in the risk of premature labour.

### THE BEST TIME TO OPERATE IN PREGNANCY

All pregnant women with pHPT need to be managed by a team including an endocrinologist, an obstetric physician, an obstetric anaesthetist and a parathyroid surgeon experienced in complex parathyroid disease. The best available evidence suggests that asymptomatic women with an apparently uncomplicated pregnancy and mild hypercalcaemia (i.e. up to 0.25mmol/l above the upper limit of normal) may be managed with conservative

outpatient measures alone. The women who remain stable and asymptomatic may optimally undergo parathyroidectomy post-partum, ideally before a subsequent pregnancy!

*‘Given the greater background miscarriage rate in the first trimester, the second trimester is universally accepted as the most favourable time to intervene, with the greatest benefit to the woman and fetus.’*

Women with significant hypercalcaemia (serum calcium 0.25mmol above the upper limit of normal), symptoms or pregnancy complications related to pHPT should undergo surgery. The decision to offer parathyroid surgery should be made with the informed involvement of the patient and her family. The safest time to undertake surgery is the second trimester and the exact timing is dependent on the severity of hypercalcaemia and/or symptoms. Severe uncontrollable hypercalcaemia and symptomatology prompt urgent intervention, whereas stable disease may be treated with less urgency, but also ideally within the second trimester. Surgery requires a parathyroid surgeon comfortable with the management of unlocalised disease, an anaesthetist experienced in both neck endocrine surgery and obstetric anaesthesia, and a member of the obstetric team to perform fetal monitoring before and after general anaesthesia.

### WHAT FURTHER CARE IS NEEDED?

Post-operatively, calcium monitoring and prevention of hypocalcaemia are essential, as this can also be detrimental to the pregnancy. Prophylactic oral calcium may be required in patients with severe hypercalcaemia preoperatively. The harmful effects of pHPT to the pregnancy, particularly pre-eclampsia, are not immediately reversed by curing the pHPT, and so the pregnancy should continue to be followed in an obstetric clinic. Post-partum, the mother should be referred for genetic testing, if her pHPT was present at 30 years of age or younger.

The optimal timing of parathyroidectomy in pregnancy could therefore be summarised as ideally before conception, and in moderate–severe disease at some point during the second trimester, with exact timing depending on its severity. If neither of those apply, it should be performed post-partum.

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### REFERENCES

1. Hirsch D *et al.* 2015 *Journal of Clinical Endocrinology & Metabolism* **100** 2115–2122.
2. Norman J *et al.* 2009 *Clinical Endocrinology* **71** 104–109.
3. Di Marco AN *et al.* 2019 *Journal of the Endocrine Society* **3** 1009–1021.
4. Saloojee H & Coovadia H 2015 *Lancet Global Health* **3** e342–e343.
5. Rai R & Regan L 2006 *Lancet* **368** 601–611.
6. McNair T & Altman K 2012 In *The John Hopkins Manual of Gynaecology and Obstetrics*, pp. 438–439. Philadelphia, USA: Wolters Kluwer.
7. Balinskaite V *et al.* 2017 *Annals of Surgery* **266** 260–266.

## OUT OF TIME: CIRCADIAN MISALIGNMENT AND METABOLIC HEALTH

WRITTEN BY LOUISE HUNTER

Reading this in the depths of winter, you may be looking forward to springtime and the clocks going forward. In the UK, the biannual practice of moving clock times forwards or backwards has been in place since World War I. But this may not always be the case.

In March 2019, the European Parliament voted to abolish clock changes from 2021, instead allowing countries to choose permanent winter time or permanent summer time (daylight saving time). The Society for Research on Biological Rhythms (SRBR) has published a statement advocating the abolition of daylight-saving time in the USA and, instead, the introduction of permanent standard time.<sup>1</sup>

There are arguments for and against both positions, involving road safety, farming activity and energy use. But the impact of clock time on our

metabolic and cardiovascular health is attracting increasing attention, and is one of the key arguments made by SRBR.

### BEHAVIOUR VERSUS BODY CLOCK

Clock time reflects behavioural time – the time we have to get up and go to work, move around, eat our meals and interact with others. Our location in relation to the sun determines when the sun rises, when the sun sets and how long the days and nights are in between. And it is the cycle of light–darkness which is the most potent entrainment cue (‘zeitgeber’) to our intrinsic body clock, through signals from the retina to the hypothalamic suprachiasmatic nucleus.<sup>2</sup>

Either through changes in clock time (e.g. travelling across time zones and biannual clock changes) or through uniformity of time zones across large geographical areas, behavioural time and body clock time can become misaligned. The body clock, our internal time-keeping mechanism, drives rhythms of physiology designed to match a rhythmic environment. Such behaviour–body clock misalignment can, therefore, lead to mismatches (for example) between when food is eaten and when the body is



anticipating a nutritional load, or between actual and anticipated times of physical activity.

Nightshift work and long-haul travel are obvious, extreme examples of circadian misalignment. Yet, it is argued, even the 1 or 2 hours of misalignment produced by daylight saving time (misalignment is more pronounced for people living on the edges of time zones) may have adverse effects in the longer term.

### MANIFESTATIONS OF MISALIGNMENT

In humans, circadian misalignment is associated with insulin resistance, hypertension and heart disease,<sup>3</sup> with laboratory protocols of circadian disruption reporting higher mean arterial pressure and higher circulating levels of glucose and insulin in subjects, with lower levels of leptin.<sup>4</sup> Work in mice has demonstrated altered cardiac conduction and reduced energy efficiency.<sup>5</sup> Large population studies of the metabolic impact of clock changes have yet to be undertaken, but there is literature examining activity levels and incidence of myocardial infarction.

If we are sufficiently concerned by the existing evidence, what can we do? On an individual level, awareness of behaviour patterns which conflict

with the light–darkness cycle is important. Chronobiologists recommend maximising exposure to natural daylight (which is far brighter than indoor lighting, even on dull days) when we are up and active, with a corresponding minimisation of light exposure at night. Eating meals within a limited window of the 24-hour cycle ('time-restricted eating') or, at least, avoiding meals in the late evening, is also attracting interest. But whether and how we effect societal change will be the key debate.

### LOUISE HUNTER

NIHR Academic Clinical Lecturer, Centre for Biological Timing, University of Manchester

### REFERENCES

1. Roenneberg T *et al.* 2019 *Journal of Biological Rhythms* **34** 227–230.
2. Multiple Authors 2016 *Science* **354** 986–1015.
3. Kervezee L *et al.* 2018 *European Journal of Neuroscience* doi: 10.1111/ejn.14216.
4. Scheer FAJL *et al.* 2009 *Proceedings of the National Academy of Sciences of the USA* **106** 4453–4458.
5. West AC *et al.* 2017 *Nature Communications* **8** 417.

## 24 HOURS IN THE LIFE OF A HORMONE: WHAT TIME IS THE RIGHT TIME FOR A PITUITARY FUNCTION TEST?

WRITTEN BY ANNEKE GRAF

The pulsatile nature and rhythmic pattern of hormone secretion can have important implications for the measurement of circulating hormone levels.

As many hospitals in the UK migrate to electronic patient records and ordering systems, it is all too easy to click on pre-ordered pathology panels, and not pause to consider what is actually being requested. Pathology tests taken at the wrong time of day waste resources, cause inconvenience and can provoke anxiety for health professionals and patients alike when trying to interpret unhelpful results.

Having an understanding of the pattern of pituitary hormone secretion will guide us in determining the optimal time to order these investigations. Here, I summarise issues relating to some common endocrine blood tests, to serve as a reminder to 'think before we click' when ordering tests.

### GROWTH HORMONE

Generally, ordering a random growth hormone (GH) level is unhelpful; the results will be difficult to interpret. Frequent blood-sampling techniques have demonstrated the pulsatile nature of GH secretion, with approximately eight peaks per 24-hour period, predominately at night. Between pulses, the serum GH concentration may be undetectable.<sup>1</sup>

Numerous other endogenous and exogenous factors (e.g. age, sex, weight, sleep, food, stress and exercise) influence the complex regulatory mechanism of the GH axis.<sup>2,3</sup> Given that 5- to 20-minute sampling for

24 hours is not practical, we usually rely on dynamic testing to investigate GH excess (oral glucose tolerance test) or deficiency (e.g. insulin tolerance test or glucagon stress test).

### THYROID FUNCTION TESTS

The timing of phlebotomy is not usually considered when ordering thyroid function tests. Circadian variation in thyroid-stimulating hormone (TSH) levels has been well described, with secretion partially pulsatile and partially basal. TSH concentrations are maximal overnight and lowest in the late afternoon to early evening.<sup>4,5</sup> Despite this, thyroid hormone levels do not rise significantly after an overnight TSH surge, possibly because overnight TSH molecules are less bioactive than those circulating in the day.<sup>6</sup>

A TSH measurement at 09.00 has been shown to strongly correlate with the total 24-hour TSH secretion, sampled at 10-minute intervals.<sup>7</sup> The circadian differences in secretion may cause a small variation in TSH levels – in older literature a mean of 0.95–2 mIU/l – although generally this does not result in TSH values outside the normal reference range.<sup>8</sup>

Thus, the timing of a TSH sample may only be of relevance if treatment decisions are being based on minor changes in TSH level.

### FEMALE REPRODUCTIVE HORMONES

The fluctuations of female reproductive hormones within a single day are not usually considered when interpreting test results, but these hormones do exhibit endogenous circadian regulation. Oestradiol, progesterone, follicle-stimulating hormone (FSH) and luteinising hormone (LH) show significant 24-hour rhythms during the follicular phase of the menstrual

Pituitary hormone/test	Secretion pattern	Timing of the test
Growth hormone	Pulsatile secretion	Random GH levels are difficult to interpret. Use dynamic testing or insulin-like growth factor 1 as a surrogate marker to circumvent hormonal fluctuations.
Thyroid function	Circadian variation in TSH levels (overnight peak, late afternoon trough). Thyroid hormone levels do not change significantly with this variation.	There is only small variation in measured TSH levels. Timing of sampling is only of clinical relevance if treatment decisions are being based on minor changes in TSH levels.
Female reproductive hormones	Significant 24-hour rhythms, particularly during the follicular phase of the menstrual cycle. Peaks occur at different times of the day for various hormones.	Useful to consider when interpreting results, but unlikely to alter the time we order the test.
Male reproductive hormones	Testosterone has a diurnal secretion pattern (morning peak, early evening trough).	Morning sampling helps limit the effects of diurnal variation, particularly in younger men.
Cortisol	Diurnal rhythm	08.00–09.00 sample or dynamic test.
Prolactin	Circadian variation with major nocturnal elevations, particularly associated with the onset of sleep.	A sample taken first thing in the morning may still reflect the nocturnal prolactin peak.

cycle. In contrast, only FSH is significantly rhythmic during the luteal phase. The hormonal peaks have been found to occur in the morning for progesterone, in the afternoon for FSH and LH, and during the night for oestradiol.<sup>9</sup>

These findings are unlikely to alter the time of day we order female reproductive hormone measurements. However, they are useful to consider when interpreting test results alongside factors we regularly take into account, such as menstrual cycle phase or menopausal status.

## TESTOSTERONE

Testosterone secretion has a diurnal pattern of secretion. Peak levels are reached in the morning between 07.00 and 10.00, a trough is seen in the evening and levels then begin to rise again at night.<sup>10</sup> One study found young men (30–40 years old) to have average 08.00 testosterone levels (both free and total) that were 30–35% higher than levels measured in the mid- to late afternoon. This difference declined with age, dropping to approximately 10% at 70 years of age.<sup>11</sup> This blunting of the circadian rhythmicity of testosterone with normal ageing has been well described.<sup>12</sup>

Sampling testosterone in the morning may limit the effects of diurnal variation, and current recommendations are to check a 08.00–09.00 testosterone level, along with sex hormone-binding globulin.

In terms of monitoring testosterone replacement, it depends on the product used. Recommendations from the product information sheet vary from clinical recommendations. For example, product sheets suggest checking testosterone levels pre-application for Testogel® and Testim®, and 2 hours after application for Tostran®. In clinical practice, it is often advised to check testosterone concentration 4–6 hours after application.

## CORTISOL

It is well known that cortisol has a circadian rhythm, with levels peaking in the morning between 08.00 and 09.00, and smaller secondary peaks after meals.<sup>13,14</sup> This diurnal rhythm can be affected by sleep and working night shifts.

Since the advent of the newer cortisol assays, we often see a low afternoon cortisol, and endocrinologists are frequently asked to assess hypothalamic-pituitary-adrenal (HPA) function. There is good concordance with 09.00 cortisol as a starter to define HPA function, which is why we generally advise standardised 09.00 cortisol measurement first off.<sup>15</sup> However, if this does not yield an answer, it may be necessary to move to stimulatory tests, such as a synacthen test or insulin tolerance test.

## PROLACTIN

When interpreting a single sample showing a mildly raised prolactin level, we often take into consideration external factors (such as stress or certain medications), but rarely the diurnal variation of prolactin secretion.

Prolactin is secreted in a circadian and pulsatile pattern with major nocturnal elevations. Sleep onset is rapidly followed by an increase in prolactin secretion, and awakenings coincide with an immediate offset of secretion.<sup>16,17</sup> Hence, the highest levels occur in the early hours of the morning. A sample taken first thing in the morning may still reflect the nocturnal prolactin peak, and repeating the sample later in the day may yield a different result.

## ANNEKE GRAF

Department of Endocrinology, University College London Hospitals NHS Foundation Trust

## REFERENCES

- Plotnick LP *et al.* 1975 *Journal of Clinical Endocrinology & Metabolism* **40** 240–247.
- Veldheis JD *et al.* 2008 *Endocrine Reviews* **29** 823–864.
- Murray PG *et al.* 2015 *Journal of Endocrinology* **226** T123–T140.
- Brabant G *et al.* 1990 *Journal of Clinical Endocrinology & Metabolism* **70** 403–409.
- Ehrenkranz J *et al.* 2015 *Thyroid* **25** 954–961.
- Persani L *et al.* 1995 *Journal of Clinical Endocrinology & Metabolism* **80** 2722–2728.
- Roelfsema F *et al.* 2014 *Journal of Clinical Endocrinology & Metabolism* **99** 570–578.
- Keffler JH 1996 *Clinical Chemistry* **42** 125–134.
- Rahman SA *et al.* 2019 *Journal of Clinical Endocrinology & Metabolism* **104** 6049–6059.
- Gall H *et al.* 1979 *Andrologia* **11** 287–92.
- Brambilla DJ *et al.* 2009 *Journal of Clinical Endocrinology & Metabolism* **94** 907–913.
- Plymate SR *et al.* 1989 *Journal of Andrology* **10** 366–371.
- Newell-Price J *et al.* 2008 *Clinical Endocrinology* **68** 130–135.
- Bhake RC *et al.* 2019 *Journal of Clinical Endocrinology & Metabolism* **104** 5935–5947.
- Mackenzie SD *et al.* 2019 *Clinical Endocrinology* **91** 608–615.
- Spiegel K *et al.* 1994 *Sleep* **17** 20–27.
- Saleem M *et al.* 2018 *Clinical Biochemist Reviews* **39** 3–16.



# In 2019 TOGETHER WE ACHIEVED

## Recruiting the NEXT GENERATION



Funded **12 Summer Studentships** to encourage students to do laboratory research

Held the **third National Endocrinology and Diabetes Taster Day** jointly with YDEF to encourage trainees to choose endocrinology

## Setting the HIGHEST STANDARDS

Published joint **Position Statements** on **safe treatment of hyperprolactinaemia** and against recent treatment recommendations for **subclinical hypothyroidism**



Impact factor  
**4.381**  
Journal of Endocrinology

Impact factor  
**4.774**  
Endocrine-Related Cancer

Impact factor  
**3.744**  
Journal of Molecular Endocrinology

Impact factor  
**2.915**  
Endocrine CONNECTIONS

Impact factor  
**2.897**  
CLINICAL ENDOCRINOLOGY

Recommended a **minimum 2 years' protected specialty time** for Endocrinology and Diabetes trainees to better equip future endocrinologists



Keep growing  
**WITH US**

## Supporting CAREER DEVELOPMENT AT ALL STAGES

Refocused the SfE BES conference programme around our **Endocrine Network communities**, with **new innovation** and **skills sessions**, to support our members' career development



Launched our **Leadership and Development Awards Programme** to recognise emerging talent and provide further opportunities for career progression for 12 outstanding members



Supported **5 Nurse Members** to undertake a Masters-level module in Endocrine Nursing

## Enabling people to make BETTER DECISIONS ABOUT THEIR HEALTH



Continued to promote **accurate science** in the media, by tackling misinformed stories in *The Times* and *The Guardian* and provided **expert advice** to routine journalist queries

Introduced **11 new content editors** to work with the **You and Your Hormones editorial board** to ensure dissemination of accurate information on a broader range of hormone-related subjects



## Collaborating within THE ENDOCRINOLOGY COMMUNITY

Established a new Endocrine Network: **Endocrine Consequences of Living with and Beyond Cancer**



Introduced a new online platform, **SfE Connect**, to facilitate **member communications** and **enhance idea sharing**

## Be at the forefront of endocrinology **WITH SOCIETY JOURNALS**

We publish cutting-edge research and best practice in the field of endocrinology through our five official journals and conference abstracts.

As well as free access to Society journals through the Members' Area of the website, don't forget that you are also entitled to:

- 40% discount to publish in *Endocrine Connections*
- Discounted fees to publish in *Endocrinology*, *Diabetes and Metabolism Case Reports*
- No colour or supplementary data charges for publishing in *Journal of Endocrinology*, *Journal of Molecular Endocrinology* and *Endocrine-Related Cancer*
- Discounted author publication charges to publish Open Access in *Clinical Endocrinology*



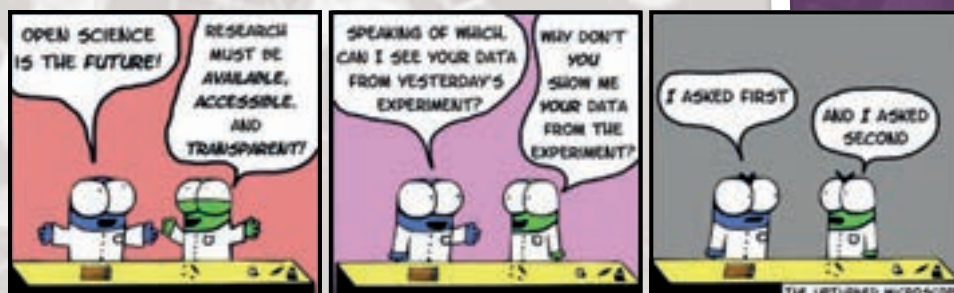
Follow **@ClinEndocr**, the new *Clinical Endocrinology* Twitter account for links to papers, archive highlights and to join the conversation in journal clubs.



Find out more at [www.endocrinology.org/publications](http://www.endocrinology.org/publications)



## Do you want to star in a comic strip?



*Journal of Molecular Endocrinology* is offering its authors the chance to win a personalised comic strip, based on their research.

To enter, all you need to do is summarise your paper in three pertinent/exciting sentences that tell the story of your work, and send it to us by **31 March 2020**.

Find out more at:  
<https://tinyurl.com/JMEComic>



# Events & TRAINING 2020

Society events enable attendees to exchange knowledge, share experiences and strengthen collaborations across a global community of endocrinologists.

Learn about your opportunities at: [www.endocrinology.org/events](http://www.endocrinology.org/events)

## National CLINICAL CASES

12  
MAR

📍 Royal Society of Medicine, London

### Clinical Case Submission Deadline

Wednesday 22 January 2020 (11:59 pm GMT)

## Endocrine ACADEMY

20–22  
APR

20–21  
APR

21–22  
APR

📍 Hilton Birmingham Metropole Hotel

CU

ENU

CDW

This event brings together **Clinical Update (CU)**, **Endocrine Nurse Update (ENU)** and **Career Development Workshop (CDW)**.

### Clinical Update

Clinical case deadline: Thursday 30 January (11:59 pm GMT)

Early bird registration deadline: Thursday 27 February (11:59 pm GMT)

### Career Development Workshop

Application deadline: Thursday 30 January (11:59 pm GMT)

## National Training Scheme FOR THE USE OF RADIOIODINE IN BENIGN THYROID DISEASE

2020

📍 United Kingdom

## SfE BES 2020

📍 Harrogate Convention Centre

16–18  
NOV

## Brilliance in Brighton AT SfE BES 2019



Our 38th annual Society for Endocrinology BES conference was held in the vibrant city of Brighton on 11-13 November. The event attracted more than 1,150 attendees over 3 days for the very best clinical and scientific endocrine research across the discipline.

The SfE BES conference 2019 saw the introduction of a fresh programme format, focusing on each of the endocrine subspecialties and their Endocrine Network communities. The new SfE Theatre, in the centre of the exhibition hall, provided an energising platform for diverse presentations, including oral posters, Society initiatives and even a book launch.

The conference kicked off with our first 'What is new?' sessions from Caroline Gorvin and John Newell-Price. Caroline summarised papers that she felt had had the most impact on basic endocrine research over the last year. These encompassed progress in identifying genetic factors for obesity risk, an improved method for gene editing, new liver organoid models and how better environmental enrichment, through driving cars, reduces stress in lab rats!

In the second session, John summarised a selection of clinical publications that have helped improve clinical knowledge during 2019. These included advances in the diagnosis and treatment of diabetes insipidus, adrenal insufficiency, osteopenia and various thyroid conditions, with some implications for changing health policies.

**182,000**  
estimated  
Twitter reach for  
#SfEBES2019

**1,479**  
tweets used  
#SfEBES2019



“My first time at SfE BES. Found it really so enriching. Gives you so much knowledge, innovations, the new face of endocrinology.”

**533**  
abstracts  
submitted

**437**  
posters  
presented

**36**  
oral  
communications

“First time and this has opened my eyes to endocrinology.”

**899**  
registered users  
on the App

This year's debate was a real highlight, where John Wilding and Sadaf Farooqi hotly contested the house view that 'nature not nurture determines our body weight'. Before arguments, the room was 64% in favour of 'nurture' being the main factor in deciding body weight. However, after Sadaf's compelling evidence, and despite John Wildings' valiant counterpoints, the room ended up just 47% in favour of 'nurture' being the most important element, with a number of people changing their mind to believe that 'nature' is the predominant factor in determining body weight.

On Monday evening, delegates had the chance to mingle at the Welcome Reception, whilst some Early Career and Nurse Members had a night of jovial inquiry at the Curry and Quiz. For those lucky enough to secure a conference dinner ticket, there was plenty of fun to be had on Brighton Pier, with unlimited access to the fairground rides, followed by drinks and fish and chip canapes and a delicious two-course dinner.

You can view more SfE BES 2019 photos on our Facebook page [facebook.com/SocietyforEndocrinology](https://www.facebook.com/SocietyforEndocrinology).

**1,155**  
delegates  
attended

“Looking forward to next year.”

Over **530**  
press articles on  
SfE BES 2019

“I like the simplified timetable.”

**23**  
posters presented  
in the new SfE  
Theatre

## SAVE THE DATE

Society for Endocrinology BES 2020  
Harrogate, UK, 16-18 November  
[www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2020](http://www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2020)

*\*Quotes are taken from delegate feedback*

# Working for you

## COMMITTEE SUCCESS IN 2019

All of the Society's committees have had a busy year working on a number of initiatives to benefit our members, as well as enhancing research and practice in endocrinology. We've highlighted some of their major activities here.

### SCIENCE COMMITTEE



- Awarded 18 Early Career Grants to support research projects up to a value of £10,000
- Supported the development of further initiatives to help the Society attract and retain research scientists.
- Streamlined and enhanced the Career Development Workshop programme for 2020 to include public engagement training
- Organised a session and participated in the BNA Festival of Neuroscience

“I am proud to be involved in overseeing Society grants and providing excellent programme suggestions for SfE BES, to help advance endocrine research and support the best and brightest scientific talent.”  
*Chris McCabe, Chair*

### CLINICAL COMMITTEE



- Published joint Position Statements on safe treatment of hyperprolactinaemia and against recent treatment recommendations for subclinical hypothyroidism
- Recommended 2 years' minimum protected specialty training time for Endocrinology and Diabetes, which has been acknowledged by the GMC
- Conducted Interdepartmental Peer Review within three centres, with discussions on how to most effectively share best practice and link with other clinical quality initiatives such as Getting It Right First Time (GIRFT)
- Established a new working group looking at genetics in endocrinology that aims to develop a series of short guidance documents to ensure easy access to information and education

“Being part of a committee has fine-tuned my non-clinical skills and has brought many ideas back to my local hospital trust, benefiting my patients and colleagues.”  
*Stephanie Baldeweg, Chair*



## NURSE COMMITTEE



- Developed an evidence guide to support the *Competency Framework for Adult Endocrine Nursing* to assist endocrine nurse training. The guide gives examples of the evidence that can be utilised to meet the requirements of each level of competence from competent through to expert
- Started work on developing the third edition of the Framework to include further competencies as well as gaining feedback on format and usability
- Made funds available to cover tuition costs to encourage nurses to complete the Oxford Brookes Masters-level module in endocrine nursing. Grants have been awarded to five nurses who are just starting their training
- Established a collaborative relationship with the European Society of Endocrinology Nurse Committee to allow sharing of best practice
- Formed a working group to produce a Position Statement that outlines best practice for nurse training

“I am proud to represent the voice of nurses academically, helping to develop the Society and contribute to its growth and future success as an organisation.  
*Anne Marland, Chair*

## EARLY CAREER STEERING GROUP



- Developed a new video prize for undergraduate students to help inspire them to pursue endocrinology
- Developed collaborative relationships with the European Society of Endocrinology Young Endocrinologists and Scientists (EYES) group
- Coordinated, in partnership with YDEF, the delivery of a third National Endocrinology and Diabetes Taster Day for medical trainees
- Successfully organised a symposium at SfE BES 2019 together with a number of networking initiatives for early career endocrinologists and piloted a 'CV clinic'

“I have seen our suggestions recognised, which is very rewarding.  
*Kate Lines, Chair*

## PUBLIC ENGAGEMENT COMMITTEE



- Established new editorial board and content editors for *You and Your Hormones*
- Co-ordinated a series of public events including the Big Bang Fair in Birmingham, Swansea Science Festival and Café Scientifique in Brighton – reaching approximately 1,000 people and providing opportunities for members to volunteer in different parts of the country
- Inspired 70 key stage 4 students at our schools outreach event held at SfE BES conference
- Worked with British Science Week to put together teaching activity packs to engage students with hormone science

“We are committed to building the Society's reputation as a trusted and go-to place for accurate information on hormones.  
*Maralyn Druce, Chair*

**We are regularly looking for new members at all career stages and from all backgrounds to sit on our committees. If you're interested, keep an eye out for upcoming vacancies.**



## CONTINUE YOUR CONVERSATION ONLINE...

Use the Society's new  
online community tool,  
**SfE CONNECT**, to  
share knowledge and  
best practice.



## SfE CONNECT

- Inform other members about what's new in your field
- Get advice or expertise from Endocrine Network members
- Promote new posts or meetings of interest to Endocrine Network members
- Discuss any issues relevant to your work and the wider endocrine community

Join **SfE CONNECT** to access exclusive Society for Endocrinology BES conference 2019 news and views and continue the conversation

[www.endocrinology.org/join-sfe-connect](http://www.endocrinology.org/join-sfe-connect)

**PROUD GOLD SPONSORS OF SFE BES 2019**

Thank you to all who attended the HRA Pharma  
Rare Diseases-sponsored symposium

# COLLECTIVE THINKING:

Can greater collaboration improve outcomes  
in Cushing's syndrome?

**Chair: John Wass**

**Speakers: Menai Owen-Jones, John Newell-Price, Joan Grieve**

**We look forward to supporting the Sfe BES again next year**



# Let us help strengthen **YOUR CLINICAL PRACTICE AND SERVICES**

The Society's free Interdepartmental Peer Review scheme aims to review all specialist endocrinology centres in the UK. Take part now in this great opportunity to exchange ideas to help strengthen endocrinology, improve networking and promote good practice.



## Join in our voluntary, supportive and non-confrontational review of clinical governance and service delivery to:

- help support the changes your unit needs
- reflect on the effectiveness of your current practice
- recognise your centre's achievements and build team morale
- provide impartial reassurance to patients of service quality

Applications from all endocrine centres are now welcome for 2020/21 visits.

Contact:  
**natasha.archer@endocrinology.org**  
for further information and to book a review.

“ We have had two new consultants, and one retirement. It was useful to have the review at a time of change to help us prioritise service development.

“ We often feel a bit isolated ... so it was reassuring to learn we're actually doing quite well!

“ Many thanks to the reviewers for their supportive attitude and for stimulating discussion.

“ Enabled some deficiencies to be highlighted to colleagues in multi-disciplinary teams, i.e. a lever for change.

“ I believe the visit was very important – our MD and CEO used the report to lobby primary care trusts whenever they had a chance.

“ Excellent report captured all the current issues within our department and the city as a whole.

“ It actually took less time than I thought to do the self-assessment questionnaire! The time has not been excessive and it has helped us concentrate on ourselves, which often you don't get the time to do.



“ This has been a very worthwhile experience and is highly recommended. It is non-threatening, constructive and informative, delivered with understanding of the real issues at the grass roots of clinical care.



Visit [www.endocrinology.org/clinical-practice/interdepartmental-peer-review](http://www.endocrinology.org/clinical-practice/interdepartmental-peer-review) for more information

## INTERDEPARTMENTAL PEER REVIEW: A NURSE'S PERSPECTIVE



WRITTEN BY PHILLIP YEOH

I have worked in endocrinology for over 20 years, but this was my first time as a peer reviewer for endocrinology centres in UK.

Our team consisted of two consultants and two endocrine nurses. Essentially, the peer reviewers' task is to look at each centre to appraise the merits of what it has achieved and to provide recommendations for improvement.

I was intrigued to see whether the endocrine nurses there worked differently from my nursing team. It was lovely to meet nurses that I have not seen for many years, and it brought sweet memories of our collective work from the past.

Prior to the peer review, each centre is required to complete a self-assessment form from the Society for Endocrinology. The form asks for detailed information about each centre. The task of the peer review team is to look for evidence of what is listed on the self-assessment form. From the viewpoint of a novice reviewer, the focus is on the experience and journey of people with an endocrine condition, as well as the relationship within the team in each centre. The opinions of the reviewers need to strike a balance between the standard of care and the challenges each centre faces. The process also highlights areas where each centre has experience and the issues they have to address.

My feeling is that the better resourced and bigger centres often attract larger pools of talent. In this situation, sharing experiences with smaller centres is vital to ensure that smaller endocrine units are not left behind in providing a good standard of care for their endocrine patients.

Many centres share similar challenges. One area that requires urgent attention is the training of new endocrine nurses. From my personal experience, recruiting an endocrine nurse is a formidable task. One can forget about finding an experienced endocrine nurse when recruiting, as they are a rare breed. I usually recruit from other areas, such as diabetes, ENT or neurosurgery.

Retaining an endocrine nurse is even more challenging, as there are so many specialised areas for a nurse to choose from. Endocrine nursing is such a complex discipline. Unlike diabetes nurses, who tend to focus on diabetes, an endocrine nurse needs to become competent in many areas, such as the adrenal, pituitary, thyroid, parathyroid, late effects, endocrine cancers, etc., before he or she chooses to become an expert in a particular part of the discipline.

The endocrine nurse network we have within the Society for Endocrinology is second to none. We are very lucky that, in the UK, nurses have a strong presence in most health disciplines. We add value to how we look after our patients. In endocrinology, we have the *Competency Framework for Adult Endocrine Nursing*<sup>1</sup> as well as our first endocrine nursing textbook, *Advanced Practice in Endocrinology Nursing*<sup>2</sup> to guide and advance our development.

Returning to my observations as a new peer reviewer, I believe there are many areas that we can benchmark in order to learn from each other: my favourite phrase is 'not to reinvent the wheel'. The Society also has an endocrine nurses' Facebook group, where we post questions or queries to each other. We share our experiences and resources, for example about performing dynamic function tests, tools we use in the clinical setting or clinical pathways we use for our endocrine patients. This method of sharing is vital for us to progress and advance together.

I am glad that my first peer review work was supported by an experienced peer reviewer from endocrine nursing. It was only when we all sat together and discussed each of the areas we had reviewed that we got a better sense of the big picture, and identified the service development needs of the centres.

My experience with the peer review team also gave me an opportunity to reflect on my practice and how my team can develop. It was an excellent opportunity to see what is happening outside my organisation, to benchmark and to learn from others. I am very grateful for the opportunity given to me by the Society for Endocrinology. I would encourage anyone who has never done a peer review to take up the opportunity.

PHILLIP YEOH

Consultant Nurse, Endocrinology and Diabetes, The London Clinic

### REFERENCES

1. Kieffer V *et al.* 2015 *Endocrine Connections* **4** W1–W17.
2. Llahana S *et al.* 2019 *Advanced Practice in Endocrinology Nursing* Cham, Switzerland: Springer Nature.

## ANNE MARLAND

### NURSE COMMITTEE CHAIR



As we approach the festive period, we can reflect on another year gone by. It has been a year to celebrate for endocrine nursing, with successful innovations coming to fruition, as we welcome our first five students onto the Masters course. Good luck to all of them!

Back in the spring, Endocrine Nurse Update was an amazing success, and the recent Society for Endocrinology BES conference in lively Brighton was full of outstanding lectures and rooms full to capacity, with delegates squeezing in. The first nursing social was a great success, and much fun was had in the quiz. Planning is underway for the 2020 endocrine calendar of events. Please feed back to us about ways of enabling an even better experience.

How we practise professionally is a cycle of reflection and evidence-based learning/application. The importance of peer review is irrefutable. Philip Yeoh writes eloquently here about his experience of being a peer reviewer in the Society's Interdepartmental Peer Review programme. I encourage you all to embrace a peer review or to volunteer to be part of the review team.

I finish with the sad news of the untimely passing of Nikki Kieffer. As mentioned on page 3, Nikki was very much involved in the development of endocrine nursing. A full obituary will appear in the next issue.

I wish you a peaceful Christmas.

ANNE MARLAND

# BETTER TOGETHER: THE SPECIALIST ENDOCRINOLOGY CLINICAL REFERENCE GROUP

WRITTEN BY STEVE BALL

Healthcare is a complex system. Healthcare providers work with Clinical Commissioning Groups, consortia and national commissioning bodies to deliver a blend of local and specialist services. Working above and across these groups is NHS England/NHS Improvement (NHSE/I), acting as the over-arching governing body, balancing strategic responsibilities with high level operational oversight.

Within these apparently individual elements move the professional bodies (such as the Royal Colleges) and special interest groups (including the Society for Endocrinology). Their role is to inform, influence and raise awareness of emerging important issues.

The challenge is how to encourage such a complex system to work better, while avoiding the trap of a 'command and control' approach that can stifle innovation and threaten the autonomy and self-determination that are key attributes of the high-performing individuals and organisations within it.

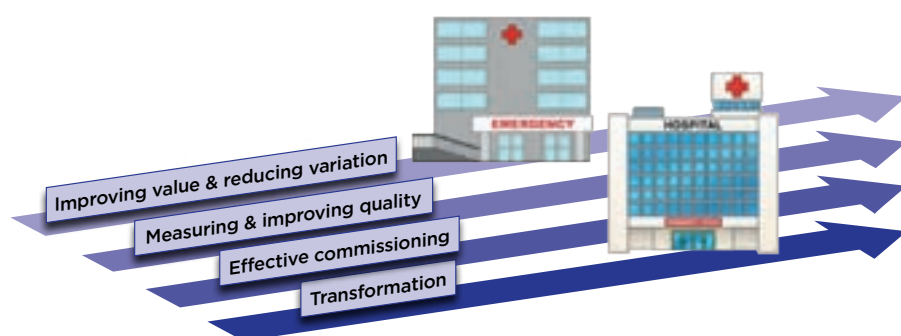
One well-trodden path would be to seek further structural change. Yet, we know that, within complex systems, such change may fail to deliver the desired outcome. We need to resist the assumption that there is a structural solution to a process problem. So, what is the way forward? How can we encourage our complex healthcare system to get better?

Working from within, rather than from outside, the system, clinical reference groups (CRGs) and the Getting It Right First Time (GIRFT) programme look to deliver the horizontal and vertical co-ordination that will enable the system to improve at pace and at scale: leading to improvement aligned with shared strategic priorities and shared standards.

CRGs are uniquely positioned to fulfil this role through their composition and relationships. While CRGs exist to support NHSE/I in 'business-as-usual functions', they are also sensitive and responsive to the wider system. They are made up of commissioners, topic experts and service user group representatives. They speak the language of all key stakeholders and can gather both the national and the local intelligence that is required to improve outcomes and experience for patients.

The Specialised Endocrinology CRG is chaired by Neil Gittoes (Birmingham). The CRG has four workstreams. Within these there are currently a number of strands, each assigned a priority and timeline:

1. Measuring and improving quality: including workforce
2. Supporting effective commissioning
3. Improving value and reducing variation
4. Transformation



An over-arching clinical priority for the CRG is to support the introduction of new or revised pathways of care across specialised and non-specialised units, to facilitate joined-up working across geographical areas. We also recognise the importance of working beyond endocrinology and linking to other CRGs. For the year 2019/20, the focus is on pathways for adrenal cancer and for total pancreatectomy and islet auto-transplantation for patients with chronic pancreatitis.

As we move forward, the CRG will be an important agent of change within the system. Its success hinges on wide engagement. To this end, the intention is to make the CRG visible and for its processes to be transparent.

We very much want to be approached by clinicians and professional groups with ideas. Please get in touch in person or by email:

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STEVE BALL  
Society for Endocrinology Representative,  
Specialised Endocrinology CRG

# Remembering IAN HENDERSON



Professor Ian Henderson was an internationally recognised scientist. His contributions to the field of endocrinology and to all those he trained are enormous.

Ian made major scientific discoveries and was also a tremendous servant to the scientific community through his international collaborations, his organisation of international conferences and, in more recent years, as co-Editor-in-Chief of *Journal of General and Comparative Endocrinology*. He was an active member of the Society for Endocrinology, where he was instrumental, as Chairman, in establishing the post of Chief Executive Officer in 1991. All Society staff during Ian's time in office enjoyed a warm relationship with him and remember him fondly. He was incredibly supportive, especially when times were difficult.

His research work exemplified the importance of comparative studies, which allow the separation of general from specialist features, and the development of phyletic and potential evolutionary perspectives on physiological systems. While based at Sheffield University, Ian's quest for new techniques and access to novel animal models took him to the USA and, later, an important and very productive period at Ville Franche, near Nice, France. It might have been in the USA that he developed his interest

*'He was also very aware that, among human- and mammalian-centric researchers, there was massive ignorance of the diversity of species available to provide a more tractable basis for their study.'*

in horses, which much later became a significant focus of his work – particularly in the study of laminitis.

Ian was firmly committed to the view put forward by August Krogh, the Nobel Laureate, that there are particular animals of choice in which to most effectively research specific physiological processes. Like Krogh, he was also very aware that, among human- and mammalian-centric researchers, there was massive ignorance of the diversity of species available to provide a more tractable basis for their study. He did much to turn this situation around, including in his many years as a Senior Member of the Society for Endocrinology.

One of his major contributions was the inspiration and guidance he gave to the many young scientists who passed through his laboratory in Sheffield. He made it very clear what the tests of worthwhile research were: guiding principles that stand the test of time! Ian stressed that there was a need for a clearly defined research question, the generation of interpretable data, the recognition that serendipity plays a large part in research outcomes and a need not to over-interpret the results.

The underpinning concept for all studies at Sheffield was the belief that the body worked to defend physiological set points, providing the optimum conditions for survival. An additional concept, which has only more recently been accepted, was that these were set early in life and ultimately defended by the integrated actions of endocrine, neural and local regulatory pathways.

*'One of his major contributions was the inspiration and guidance he gave to the many young scientists who passed through his laboratory in Sheffield.'*

Ian's work in the Sheffield laboratory, and that of his protégés, demonstrated that these homeostatic mechanisms were already established in early vertebrates, including fish, and have been highly conserved. Accordingly, their comparative study continues to provide valuable insights into what often appears to be intractable and complex processes in mammals, including man.

Ian's son Miles recalls that, 'One of the last things he said to Jenny (his wife of 57 years) was that "we had a lot of fun." So did I, and many others, with Ian, albeit for a far shorter period than they had the privilege of enjoying together. Few who knew Ian would express anything different, and that sentence is a fitting epitaph. He was a wonderful mentor, father and husband.'



RICHARD BALMENT  
University of Manchester

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deficiency has not been demonstrated and if other aetiologies have not been excluded. Not indicated for treatment of male sterility or impotence. Monitor testosterone at regular intervals. Adjust dose to maintain eugonadal testosterone level. Experience in patients over 65 years is limited, except for lower serum testosterone with increasing age. Pre-examine all patients to exclude a risk of pre-existing prostatic cancer. Perform regular monitoring of liver and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Use with caution in thrombophilia due to risk of thrombosis. Monitor haemoglobin, and haematocrit, liver function tests and lipid profile during long-term use. Caution with/without congestive heart failure may be a severe complication in patients with pre-existing severe cardiac, renal, or hepatic insufficiency, or ischaemic heart disease. Discontinue immediately if such complications occur. Use with caution in hypertension, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken

with sodium retention due to risk of hypervolaemia/hypertension. Androgen treatment may result in impaired insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety instructions. Health professionals/users should use disposable gloves resistant to alcohol. **Side-effects:** Key common: Application site reactions (including pruritic, stinging, pain, redness, rash or erythema). Common: Increased haemoglobin, red blood cell count, and haematocrit; increased male pattern hair distribution; hypertension, gynaecomastia, peripheral oedema, and increased PSA. May cause irritation and dry skin. Prescribers should consult the summary of product characteristics for further details of side effects. **Legal Category:** POM. **Further information is available from the Marketing Authorisation Holder:** Kyowa Kirin Ltd, Golden Square Park, Colindale, TD1 10R, UK. **Date of Prescribing Information:** March 2017.

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References: 1. Tostran 2% Gel SPC. 2. Data on file.

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